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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,329	12/10/2005	Jung Moon Kim	4240-138	9719

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
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RESEARCH TRIANGLE PARK, NC 27709

EXAMINER	
MACFARLANE, STACEY NEE	
ART UNIT	PAPER NUMBER
1649	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,329	KIM ET AL.	
	Examiner	Art Unit	
	Stacey MacFarlane	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *10-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-9 and 18-22 in the reply filed on July 23, 2007 is acknowledged. Applicant elects the species of BMPs, SEQ ID NO: 1, SEQ ID NO: 14, TAT and TGF-β with traverse. The traverse of the species election is on the grounds that merely an allegation of search burden was presented. This argument has been fully considered but is not deemed persuasive because the claims are drawn to a fusion protein with domains selected from the different species claimed. For example the polypeptide can consist of any one of the plurality of SEQ ID NOs from Claim 6 with any one of the plurality of SEQ ID NOs from Claim 7. Each combination of composite polypeptide constitutes a materially different product, and each requires a separate search of the prior art. Furthermore, the tissue regeneration domains to be cleaved by the polypeptide include, for example, bone morphogenic proteins and β-amyloid. These species are not functional equivalents of each other, as evidenced by their structurally and functionally distinct properties. Applicant is reminded that if the generic claims are found to be allowable, all species would be examined.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 10-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

3. Claims 1-9 and 18-22, in so far as they read upon the elected species will be considered upon their merits.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-9 and 18-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 1 is vague and indefinite in so far as it employs the term "protein transduction domain" as a limitation. This term is appears without a reference to a precise amino acid sequence identified by a proper SEQ ID NO: one cannot determine the metes and bounds of " protein transduction domain ". Moreover, because the instant specification does not identify that property or combination of properties which are unique to and, therefore, definitive of a protein transduction domains, one of ordinary skill would not be reasonably apprised of the scope of the invention.

7. Claims 1, 3 and 4 are vague and indefinite. These claims are drawn to a polypeptide product but recite active steps: Claim 1 recites a "cleavage site ...is cleaved by the proprotein convertase to activate tissue regeneration domain in cells" and a PTD "making the polypeptide to permeate cell membranes"; Claim 3 recites the polypeptide "which has no three-dimensional stereoregularity and has no biological activity itself"; and Claim 4 recites said polypeptide "wherein the ...FAD is cleaved by proprotein convertase present in living cells". Since the claims are drawn to a product, it is unclear how recitation of these activities or affects serve to alter the product's

structure. Section § 2111.04 of the MPEP states, "claim scope is not limited by claim language ... that does not limit a claim to a particular structure". For examination purposes these steps/activities/affects of the claims are read as non-limiting inherent features of the claimed polypeptide.

8. The term "improving" in claim 21 is a relative term which renders the claim indefinite. The term "improving" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Furthermore, the language is unclear. The method is interpreted to mean "enhancing" fibrosis or cirrhosis of the organs. Examiner suggests use of language such as "a composition for the treatment of fibrosis or cirrhosis of organs" would be remedial.

9. Claims 2, 5-9, 18-20 and 22 are indefinite for depending from indefinite claims and are included in the rejection.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1-9 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2004/197867 A1 filed March 2004 and published October 2004 (hereafter referred to as the '867 publication), and further in view of US Patent 5,013, 649, issued May 1991, and Leighton et al. *The Journal of Biological Chemistry*, 278(20): 18478-18484, published May 2003. Claims are drawn to a "fusion protein polypeptide" containing (a) a protein transduction domain comprising TAT, (b) a furin activation domain comprising SEQ ID NO: 14, and (c) a non-activated tissue regulation domain comprising an amino acid sequence of SEQ ID NO: 1, which is activated by the proprotein cleavage. Dependent claims recite a composition comprising the fusion protein, for stimulating the formation or regeneration of tissue, wherein the tissue is bone or cartilage and which further comprises the instantly-elected TGF-β.

The '867 publication teaches cell-permeable osteoinductive fusion polypeptide comprising: a) a polynucleotide encoding a cell-permeable polypeptide operatively linked to, b) a polynucleotide encoding an osteoinductive polypeptide, which when expressed together promote bone growth and disc regeneration in vivo. Specifically the reference teaches a fusion protein comprising at least one cell-permeable polypeptide including the HIV-TAT of the instant claims, operatively linked to at least one osteoinductive polypeptide, including BMP-2 and/or TGF-β. The instant specification identifies SEQ ID NO: 1 as "a gene encoding hBMP2" (page 18, line 7). The '867

reference teaches that the fusion of BMP-2 with TAT allows for the polypeptides to permeate a cell membrane without cell membrane receptors (page 2, paragraph 0024).

The instant disclosure acknowledges that the '867 publication "discloses a fusion polypeptide of a bone morphogenetic polypeptide and a protein transduction domain (PTD), and a method for inducing bone formation in animals by administering the fusion polypeptide" (page 12, lines 21-23), but states that "even if PTD is used to introduce proteins into cells, it cannot be said that all the proteins are activated to show the expected bone morphogenetic potencies" (page 13, lines 3-4), and that the crux of the instant invention is that "the present inventors have found that the primary factor of the lack of efficiency in administering the previously known rhBMPs into living human beings or mammals is due to their biochemical activity" (page 14, lines 1-3).

The '867 publication does not teach a "furin activation domain" (FAD) comprising the instantly-elected SEQ ID NO: 14, which his defined within the instant specification as "a hBMP2 pro-domain" (page 18, line 10). US Patent 5,013,649 ('649 Patent) teaches a nucleic acid sequence that is 99.2% homologous to the sequence of SEQ ID NO: 14 and SEQ ID NO: 1 combined. The '649 Patent teaches that this sequence comprise the full length of the pro-protein of human BMP-2. Furthermore, the Leighton et al. reference teaches that it was well known within the art, prior to filing, that BMP proproteins are activated within the cell by furin and furin-like protein convertases at the amino acid motif RX(K/R)R (page18480, paragraph 4, lines 1-5). While the instant SEQ ID NO: 1 encodes the hBMP-2 sequence following cleavage, it is the last four amino acids of the "hBMP2 pro-domain" of SEQ ID NO: 14 that includes the RX(K/R)R

protein convertase domain as taught by the Leighton reference. The Leighton reference teaches that expression of the proprotein with this cleavable R*X*(K/R)R domain is essential for BMP procollagen C-proteinase activity (line bridging pages 18482-18483). In the absence of this cleavable domain BMP protein is expressed and secreted but has no C-proteinase activity (Figure 4).

It would have been obvious to one of ordinary skill in the art to combine the HIV-TAT protein transduction domain as taught by the '867 publication with the pro-BMP-2 sequence as taught by the Leighton reference. A skilled artisan would be motivated to combine the elements because it was known in the art that absent the R*X*(K/R)R proprotein-cleavable domain the HIV-TAT/hBMP-2 construct would be cell-permeable but the resulting secreted protein would have no procollagen C-proteinase activity. In *KSR International Co. v. Teleflex, Inc.*, the Supreme Court has stated that where there is a "pressure to solve a problem and a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense" (*KSR International Co. v. Teleflex, Inc.* 127 S. Ct. 1727, 82 USPQ2d 1385, Supreme Court, April 30, 2007). In the instant case, the problem to be solved creation of a polypeptide that is both cell-permeable and retains BMP activity. The prior art demonstrates that there are a finite number of ways to produce such a protein, and combining prior art elements according to known methods to yield predictable results is *prima facie* obvious.

Double Patenting

13. Applicant is advised that should claim 18 be found allowable, claim 21 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof and likewise, should claim 20 be found allowable, claim 22 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacey MacFarlane whose telephone number is (571) 270-3057. The examiner can normally be reached on Monday-Thursday 6:30AM-4:00 PM & ALT. Fridays, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

SNM

OLGA N. CHERNYSHEV, PH.D.
PRIMARY EXAMINER